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Random copolymerisations catalysed by simple titanium α-amino acid complexes

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α-Amino acid complexes of titanium have been applied in the synthesis of biopolymers. The complexes can be prepared under mild conditions often using hydrous procedures and result in the preparation of polylactide and polycaprolactone without the need for rigorous drying and air-sensitive handling. The complexes also prove to be excellent initiators for the synthesis of random copolymers: they are rare examples of completely air stable designed catalysts to undertake such a transformation. The composition and thermal properties of the random copolymers are also investigated.

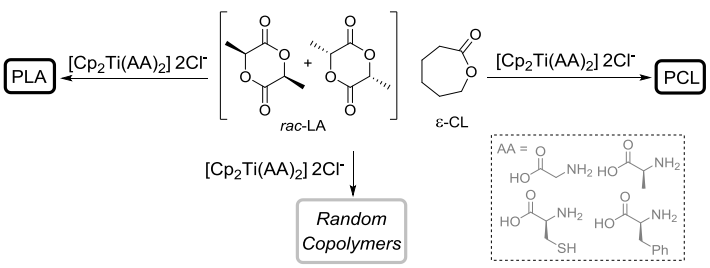
Introduction

The synthesis of biopolymers, specifically polylactide (PLA) and polycaprolactone (PCL) is a hot topic in chemistry. Several highly active metal pre-catalysts exist that furnish very high molecular weight polymer.[1] In terms of PLA, some elegant systems are also known to produce exquisite stereocontrol.[1b] The interest in these biopolymers lies in (i) the environmentally favoured route of monomer synthesis (lactide is particularly attractive in that it is essentially prepared from biomass);[1a] (ii) the biodegradable properties of the polymer (PLA can be degraded *in vivo* or in the environment in a matter of months, whilst PCL lasts somewhat longer);[1a,d] and (iii) the range of applications that these polymers have.

Much of the titanium catalysed homo-PLA and -PCL literature[2,3] is dominated by salen,[2j] aminodiol[2d,e] and bulky phenolate[3b,e] or amino phenolate[2a,b,h,i,l,3a,c] pro-ligands. There are few examples whereby very simple chiral titanium complexes have been used without the need for elaborate syntheses.[2c,m,3b,f]

Homopolymerisations initiated by Ti complexes rarely compete with the offerings made by the other metal pre-catalysts, however the merits of titanium lie in more specialised polymer applications, most notably in the synthesis of biopolymers for biomedical science. Indeed titanium proves to be a robust pre-catalyst providing access to alternative polymer systems including some rare examples of random copolymers.[4] Compared to their respective homopolymers, copolymers of PLA and PCL are viewed as advantageous in that they often have tunable properties to allow for a wider range of highly specialised applications: copolymers can range from thermoplastic to elastomeric in behaviour.[5] Effective, biocompatible methods of copolymer synthesis could lead to advances in such specialised applications as bone tissue engineering, injectable hydrogels and controlled drug release systems.[6]

The author has already shown that Ti complexes can be proficient pre-catalysts in this nascent field of copolymer synthesis.[4a] Therefore, due to the non-toxic nature of titanium, the question of whether the biocompatibility[7] could be further enhanced by incorporating simple, unmodified α-amino acid (AA) pro-ligands was raised and subsequently addressed *vide infra* (Scheme 1).



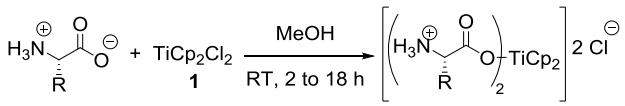
Scheme 1 Synthesis and use of Ti-AA complexes in homo- and copolymerisations

The benefits of AAs include cost: the naturally occurring L-amino acid can be purchased readily and inexpensively from commercial sources. The racemates along with the D-enantiomers are also commercially available, therefore if trends in stereocontrol are observed the opposite enantiomer can be easily investigated without need for complicated syntheses. Furthermore, some α-AA titanium complexes are already known and have shown therapeutic potential. For example Tornieporth-Oetting and White showed that α-AA complexes derived from titanocene dichloride ($TiCp_2Cl_2$) could act as broad spectrum anti-cancer agents and members of this bis(Cp)-coordinated family of titanium complexes continue to be investigated as therapeutic agents.[8,9]

PLA, PCL and their copolymers are often synthesised as potentially resorbable materials: it is therefore intuitive to look for ligands which are sympathetic to the context of use. Hence it appears that the synthesis of polymers which are well-known for their potential in biomedical applications could be enhanced if the pre-catalyst used to do so was itself biocompatible. In the field of PLA and PCL synthesis, relevant examples have been provided by Kricheldorf and Darensbourg. Kricheldorf used AA complexes of zinc for the synthesis of PLA and copolymers of LA and ε-CL at high temperatures.[10] Darensbourg has subsequently used Schiff bases derived from the amino acids L-leucine, L-methionine and L-phenylalanine to effect the polymerisation and copolymerisation of LA and ε-CL with a Zn centre.[11]

Results and discussion

Following a modified procedure from Tornieporth-Oetting,[8] α-AA complexes derived from titanocene dichloride (**1**) were synthesised in the first instance (Scheme 2). The bis-glycine (**2**),[8a] -alanine (**3**)[8a] and -cysteine (**4**)[12] complexes are formed in high yield (84%, 63% and 72% respectively). No special precautions are needed during synthesis, which is in sharp contrast to the Schlenk-line and glovebox techniques that are often required when preparing titanium complexes. The complexes can be synthesised under air using reagent grade methanol as solvent. Unfortunately, previous reports of the synthesis of the L-leucine analogue[12] failed, and only a mixture of the two starting materials was obtained. Complexes **2** to **5** are remarkably air stable: they can be stored on the bench for several months without sign of decomposition. A crystal structure of the 3-methylalanine analogue was reported previously by Tornieporth-Oetting and co-workers.[8a] Although attempts to crystallize **2**, **3**, **4** and **5** have failed thus far, based on the analytical data,[8a,12,13] it can be assumed that the desired, discrete, homonuclear titanium complexes have formed.



R = H (glycine), 84%, **2**
= CH_3 (L-alanine), 63%, **3**
= CH_2SH (L-cysteine), 72%, **4**
= CH_2Ph (L-phenylalanine), 54%, **5**

Scheme 2 Synthesis of $[TiCp_2(AA)_2]^{2+}$ $2Cl^-$ complexes

Homopolymerisations with 1 to 5

Excited by how easy these complexes are to synthesise and store, they were first tested in the homopolymerisations of *rac*-lactide and ε-caprolactone prior to exploration in random copolymerisations. The α-AA complexes were compared to results obtained for the parent titanocene complex, $TiCp_2Cl_2$ (**1**), which surprisingly does not appear to have been tested in PLA and PCL synthesis previously.[14]

Polymerisation of *rac*-LA with 1 to 5

1 performs well as a pre-catalyst for PLA synthesis: with a monomer/pre-catalyst ratio of 150:1 high M_n polymer is obtained (Table 1, Entry 1). Interestingly, when the ratio is increased to 300:1 then a further increase in M_n is observed (Entry 2). A scale-up reaction with an increased [*rac*-LA]/[Ti] ratio of 600:1 continues to produce high M_n polymer (78 924 $gmol^{-1}$) albeit in modest yield (Entry 4). These are large M_n values for a titanium-initiated system. Some other high molecular weight polymers of *rac*-lactide produced using Ti-pre-catalysts include those by Coates using diamine-diphenolate ligands[2h] where M_ns of over 100 000 $gmol^{-1}$ were observed. Davidson and Jones achieved 41 000 $gmol^{-1}$ using aminophenolate ancillary ligands,[2i] whilst an early example from Verkade achieved 119 200 $gmol^{-1}$ at the expense of PDI (2.55), but a reduction in M_n to 68 600 $gmol^{-1}$ saw PDI drop to 1.42.[2l] The results presented in Table 1 are made more remarkable by the simplicity of this commercially available pre-catalyst. It is unsurprising that the chloride ligands are able to act as the site of initiation for polymerisation, as this has been shown by several research groups.[15] End group analysis proved it likely that chloride was the initiating group, where the acyl chloride is not visible spectroscopically or is replaced with a methyl ester on quenching of the reaction with MeOH.[13]

Exchanging the chloride ligands for α-AA residues, unfortunately, does not produce higher M_n polymer. However, respectable M_n polymer is achieved with glycine adduct **2** (Entry 5). Increasing steric bulk to L-alanine reduces the M_n, which is further reduced when L-cysteine is introduced (Entries 7 and 9). Interestingly, introduction of bulky L-phenylalanine adduct (complex **5**, Entry 11) has a positive effect on M_n suggesting that electronic effects may also control the ability to polymerise. A change in ligand has an effect on stereocontrol, where a very slight heterotactic (Entry 5) or isotactic (Entry 9) is observed. Although the lack of stereocontrol is disappointing, these inexpensive, readily available pro-ligands do, nonetheless, produce competent pre-catalysts.

The ability to polymerise is evidently related to the AA residue. It was questioned whether addition of EtOH could invoke immortal polymerisation, therefore the addition of two equivalents of EtOH was explored. Addition of EtOH to **1** has a detrimental effect on catalysis (Entry 3) and although high yield is obtained, M_n is significantly diminished. The effect of EtOH on reactions initiated by complexes **2**, **3**, **4** and **5** is clear: a decrease in M_n is observed. However, the effect on yield is variable: polymerisation with complex **3** improves dramatically from 19% to 85% (Entries 7 and 8), whereas with **4** a decrease from 83% to 50% is noted (Entries 9 and 10). Slight broadening of PDI also occurs.

Quenching the reaction of **2** and *rac*-LA after two hours shows the presence of methyl ester and carboxyl end groups (LCMS).[13] Glycine end groups are also present, but in smaller quantities, not visible by ^1H NMR. This would suggest that AA dissociation is possible and the chloride anion is able to coordinate and act as an initiation point at the Ti-centre, thus when the reaction is quenched with MeOH, hydrolysis or esterification of the acyl chloride end group occurs. The methyl ester peak is also seen in a small number of examples where EtOH is used as an additive. This indicates that transesterification processes are taking place: chain scission and redistribution of polymer occurs which forms the methyl ester on quenching the non-natural (carbonyl) terminus.[13] These transesterification processes can result in the formation of oligomers, cyclic oligomers and shorter or longer polymer chains.[16] Polymerisation is taking place at relatively high temperatures with a metal known to undergo transesterification, which may provide an explanation. However, it must be noted that the vast majority of polymerisations are unimodal in nature (GPC trace).

Quenching the reaction of **2** and *rac*-LA in the presence of EtOH gives ethoxy end groups, with limited amounts of AA end

groups. This also suggests that AA displacement and ethoxide and chloride coordination is taking place. Interestingly after two hours, only 5% *rac*-LA has reacted in the absence of EtOH, whereas 90% of the monomer has reacted in the presence of EtOH. This indicates that when ethoxide forms a ligand for coordination-insertion it leads to more rapid formation of polymer, but also causes termination events to occur more readily (based on low M_n values observed). The active species (*i.e.* $Cp_2Ti(OEt)_2$) must only form at higher temperatures. Reaction of complex **2** at 100 °C in excess EtOH results in a distinctive colour change (from bright yellow to pale orange) within one hour. This does not occur at room temperature. The newly formed species is now highly soluble in $CDCl_3$. Analysis by ^{1}H NMR spectroscopy appears to show loss of the AA residue (an insoluble precipitate forms during the reaction) and coordination of ethoxide ligand occurs.[17] There is also more than one Cp signal present. This suggests that at the polymerisation reaction temperature displacement of the AA is possible.

Table 1 PLA synthesis using complexes **1** to **5**

Entry	Pre-cat.	Yield (%)[a]	M_n (gmol^{-1})[b]	$M_{n(th.)}$ (gmol^{-1})[c]	$M_{n(corr)}$ (gmol^{-1})[d]	PDI[b]	P_m[d]
1[e]	**1**	75	58 970	8 140	34 200	1.34	0.50
2	**1**	71	95 140	15 380	55 180	1.37	0.51
3[f]	**1**	98	3 800	10 640	2 200	1.46	0.52
4[g]	**1**	53	78 920	22 950	45 780	1.28	0.51
5	**2**	92	16 990	19 920	9 850	1.17	0.44
6[f]	**2**	75	9 200	8 150	5 340	1.23	0.55
7	**3**	19	10 180	4 140	5 900	1.02	—
8[f]	**3**	85	6 020	9 230	3 500	1.12	0.51
9	**4**	83	7 770	17 980	4 500	1.14	0.54
10[f]	**4**	50	7 210	5 450	4 180	1.25	0.55
11	**5**	96	12 990	20 790	7 530	1.15	0.51
12[f]	**5**	98	4 500	10 640	2 610	1.37	0.50

Polymerisation of *rac*-LA: 130 °C, 18 h, [*rac*-LA]/[Ti] = 300, 0.3 g (2.1 mmol) *rac*-LA. [a]Isolated yield. [b]Values determined by GPC analysis. [c]$M_{n(th.)}$ = ([*rac*-LA]/2[Ti] × %PLA × 144.13 + 32.04): based on two polymer chains growing from the Ti centre, end group assumed to be MeO- (*vide infra*); with added EtOH $M_{n(th.)}$ = ([*rac*-LA]/([EtOH] + 2[Ti]) × %PLA × 144.13 + 46.08). [d]$M_{n(corr)} = M_n \times 0.58$. [d]Determined by ^{1}H NMR. [e]150:1. [f]2 equivalents EtOH added (relative to [Ti]). [g]Scale up to 1 g (6.94 mmol), 600:1, 24 h.

Polymerisation of ε-CL with 1 to 5

Investigation of ε-CL polymerisation with the same set of pre-catalysts (Table 2) indicates that the mode of polymerisation of ε-CL is not the same as that for *rac*-LA. Firstly, ε-CL does not polymerise in the presence of $TiCp_2Cl_2$. However, on the addition of two equivalents EtOH a quantitative isolated yield of polymer is observed with a reasonable M_n of 9 660 gmol^{-1}. This is reiterated with pre-catalysts **2** to **4** (Entries 3 to 8). With pre-catalyst **2** a vast improvement in both yield (from 23% to 77%) and M_n (from 2 770 gmol^{-1} to 11 150 gmol^{-1}) is observed on addition of EtOH. This improvement in yield is also observed with pre-catalysts **3** and **4** (21% to 93% and 39% to 90% respectively). However, pre-catalyst **4** does not show the same pronounced improvement in M_n: as for PLA synthesis with **4**, M_n remains almost constant with or without additive. In most cases addition of EtOH leads to a large broadening of PDI. These results compare to current literature examples from Li (39 000 gmol^{-1}, 1.16),[2b] Aida (55 000 gmol^{-1}, narrow PDI)[3e] and Bochmann (32 000 gmol^{-1}, 2.50)[3c] using phenolate ligands. Whilst simple systems presented by Bounor-Legare (43 600 gmol^{-1}, 2.12),[3b] Harada (72 300 gmol^{-1}, 2.28)[3d] achieved high M_n PCL at the expense of PDI. Okuda's early example using the titanocene half-sandwich complex, $TiCpCl_2(OMe)$ remains a leading example with high M_n (33 800 gmol^{-1}) with retention of a reasonable PDI (1.50).[3f] As with PLA, end group analysis of PCL shows the presence of methoxy, ethoxy and hydroxyl end groups by ^{1}H NMR and/or LCMS suggesting dissociation of the AA prior to the initial ring-opening step by either the chloride anion or ethoxy group.[13]

Table 2 PCL synthesis using complexes **1** to **5**

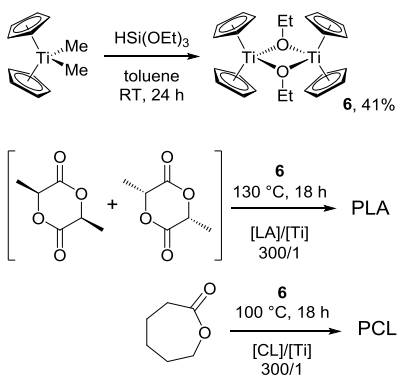
Entry	Pre-cat.	Yield (%)[a]	M_n (gmol^{-1})[b]	$M_{n(th.)}$ (gmol^{-1})[c]	$M_{n(corr)}$ (gmol^{-1})[d]	PDI[b]
1	**1**	Trace	—	—	—	—
2[e,f]	**1**	100	9 660	8 590	5 410	1.17
3	**2**	23	2 770	3 970	1 550	1.09
4[e]	**2**	77	11 150	6 620	6 240	1.45
5	**3**	21	—	—	—	—
6[e]	**3**	93	8 180	7 990	4 580	1.43
7[g]	**4**	39	3 460	6 710	1 940	1.06
8[e]	**4**	90	3 290	7 740	1 840	1.24
9	**5**	78	3 540	6 710	1 980	1.14
10[e]	**5**	90	5 840	15 440	3 270	1.14

Polymerisation of ε-CL 100 °C, 18 h, [ε-CL]/[Ti] = 300, 0.3 mL (2.7 mmol) ε-CL. [a]Isolated yield. [b]Values determined by GPC analysis. [c]$M_{n(th.)}$ = ([ε-CL]/2[Ti] × %PCL × 114.14 + 32.04): based on two polymer chains growing from the Ti centre, end group assumed to be MeO- (*vide infra*); with added EtOH $M_{n(th.)}$ = ([ε-CL]/([EtOH] + 2[Ti]) × %PCL × 114.14 + 46.08). [d]$M_{n(corr)} = M_n \times 0.56$. [e]2 equivalents EtOH added (relative to [Ti]). [f]Trimodal (M_n = 9660, 4250, 2100; PDI = 1.17, 1.03, 1.04 respectively). [g]Bimodal (M_n = 3460, 1050; PDI = 1.06, 1.17 respectively).

For both PLA and PCL many of the experimentally determined values of M_n do not match those calculated theoretically ($M_{n(th.)}$). It has been assumed that two polymer chains are able to grow from the Ti-centre, with Cp remaining intact. There is no evidence to suggest Cp is able to act as an initiation point. The discrepancy in theoretical vs. experimental M_n cannot be fully accounted for by assuming only one chain

grows from the Ti centre ($M_{n(th.)}$ = [monomer]/[Ti] × %Yield × MW) nor do $M_{n(th.)}$ calculations based on immortal conditions account for discrepancies in these reactions. It could be assumed that the rate of chain propagation is very much greater than the rate of initiation ($k_{prop.} > k_{init.}$) since application of a Mark-Houwink correction factor to the values of M_n for PLA (0.58) and PCL (0.56) also fails to account for discrepancies. Rather than fast chain transfer associated with immortal polymerisation, which should retain narrow PDI,[18] it may be that under reaction conditions displacement of the AA with ethoxide is taking place. As previously described, polymerisations carried out in the presence of EtOH have ethoxy end groups in the ^{1}H NMR spectrum.[13] Pre-catalysts **1** to **5**, each give very different yields and M_n (for both PLA and PCL) this may indicate how readily the ethoxy ligand is able to displace the different AA residues to form the active species. The decrease in PLA M_n and broadening of PDI in the presence of EtOH (Table 1, Entries 3, 6, 8 and 10) could also be a result of increased transesterification processes leading to shorter chains being formed, and hence discrepancies in $M_{n(th.)}$.

Complex **6** was synthesised using known procedures (Scheme 4)[19] and used to determine whether a titanocene ethoxide complex was capable of initiating the polymerisations and how competently it performed in comparison to the other pre-catalysts. **6** is an excellent pre-catalyst: M_n is high and competitive with the leading Ti examples, but PDI is broad. Again there is a discrepancy in theoretical and experimental results. As expected ethoxy and methoxy (transesterication) end groups are observed by spectroscopic analysis.[13] This dinuclear Ti complex is evidently a far superior pre-catalyst in homopolymerisations compared to the AA adducts.



Mon.	Yield (%)[a]	M_n [b] (gmol^{-1})	$M_{n(th.)}$ [c] (gmol^{-1})	$M_{n(corr)}$ [d] (gmol^{-1})	PDI[b]
rac-LA	97	32 900	41 940	19 080	1.55
ε-CL	100	52 150	34 240	29 200	1.67

[a]Isolated yield. [b]Values determined by GPC analysis. [c]$M_{n(th.)}$ = ([*rac*-LA]/[Ti] × %PLA × 144.13) or $M_{n(th.)}$ = ([ε-CL]/[Ti] × %PCL × 114.14): based on one polymer chain growing from the Ti centre. [d]$M_{n(corr)} = M_n$ × 0.58 or 0.56.

Scheme 4 Synthesis of **6**[19] and use in PLA and PCL synthesis

Random copolymerisations

Although complexes **1** to **6** are competent pre-catalysts for the synthesis of PLA and PCL, the activity is much lower than the well-developed Zn, lanthanide and Al systems so often reported.[1] An area of biopolymer synthesis that is growing in importance but still hugely underdeveloped is the field of random copolymer synthesis. The author has shown that titanium can form useful pre-catalysts for random copolymerisations.[4a] Very few random copolymerisations have been reported irrespective of metal and fewer still with such simple air-stable complexes. Greater research into metal-catalysed random copolymerisations is needed in order to make significant advances needed for real-life applications.

In the presence of EtOH **1** is a poor pre-catalyst for homo-PLA synthesis where reactivity is shut down and M_n is only 3 800 gmol^{-1} (Table 1, Entry 3). On the other hand, although modest, addition of EtOH to **1** allows homopolymerisation of ε-CL to proceed. In the presence of EtOH, **1** produces copolymer in excellent yield and the ratios of ε-CL to *rac*-LA are approaching the desired 50/50 ratio. It is interesting to note that average chain lengths (L_{CL} and L_{LA}) are short. On inspection of the $^{13}C\{^1H\}$ NMR spectrum[13] it is clear that transesterification has facilitated the polymerisation, indeed transesterification (represented by the distinctive signal at around 170.8 ppm) is two to three times greater in pre-catalyst **1** compared to the others tested. Pre-catalyst **5** in the absence of EtOH shows comparable copolymerization reactivity to the other pre-catalysts where EtOH is used (Entry 6), however, addition of EtOH only acts to decrease M_n (Entry 7). EtOH does have a positive effect on the copolymerisation initiated by **5** in that a 51/49 ratio of LA to CL is observed in this instance: this is a rare example where a 1:1 feedstock of monomer has produce a 50/50 mixture in the final copolymer. Average sequence lengths of LA and CL are short (2.5 and 2.3 respectively), but the transformation shows high levels of transesterification.[13] Random copolymerisation facilitated by **2**, **3** and **5** (Entries 2, 4, 5, 6) show only very modest levels of transesterification. Overall the random copolymers give better continuity between the experimental and theoretical values of M_n. Intriguingly, **6** offers no improvement on random copolymerisations even although it is an excellent homopolymerisation pre-catalyst, showing that excellence in homopolymerisation and excellence in copolymerisation can be mutually exclusive.

With a 1:1 feedstock of *rac*-LA and ε-CL, the pre-catalysts display short chain lengths of *rac*-LA approaching the ideal value for a random copolymer (L_{LL} = 2).[4e,20] It is clear from the ^{1}H NMR spectra that there are good levels of hetero-bonding in the polymers: these are not mixtures of homopolymer or block copolymer and is the case with all copolymers presented. As expected, when the ratios of ε-CL and *rac*-LA feeds are altered to 2:1 *rac*-LA/ε-CL (pre-catalyst **2**) there is an increase in the incorporation of *rac*-LA (Entry 3). There is a marked increase in average sequence length of *rac*-LA along with M_n. When the ratio is changed to 1:2 *rac*-LA/ε-CL the ε-CL incorporation is raised, but only to 60% (Entry 4). L_{CL} increases to 3.1 with L_{LL} deceasing to 1.9.

Table 3 Random copolymerisation with Ti complexes.

Entry	Pre-cat.	Yield (%)[a]	M_n (gmol^{-1})[b]	$M_{n(th.)}$ (gmol^{-1})[c]	$M_{n(corr)}$ (gmol^{-1})[d]	PDI[b]	ε-CL/ LA[e]	L_{CL}/ L_{LL}[f]	T_g (°C)[g]	$T_{g(th.)}$ (°C)[h]
1[i]	**1**	80	20 700	15 970	11 830	1.54	38/62	2.2/2.8	-14.1	-3.2
2[i]	**2**	78	12 560	15 580	7 190	1.38	38/62	2.4/3.0	-14.2	-3.2
3[i,j]	**2**	61	18 520	12 740	10 660	1.61	18/82	1.8/4.8	—	—
4[i,k]	**2**	82	20 120	16 300	11 420	1.68	60/40	3.1/1.9	—	—
5[i]	**3**	78	19 350	15 650	11 090	1.48	36/64	2.3/2.9	-12.5	-0.5
6	**5**	88	17 500	16 600	10 020	1.68	38/62	2.5/3.0	-26.2	-3.2
7[i]	**5**	98	8 430	18 990	4 810	1.76	49/51	2.3/2.5	-24.4	-17.3
8	**6**	74	16 150	27 770	9 250	1.55	36/64	2.2/2.9	-9.0	-0.5

Random copolymerisation: 130 °C, 18 h, [monomer]/[Ti] = 600, 0.3 g (2.1 mmol) *rac*-LA, 0.23 mL (2.1 mmol) ε-CL. [a]Isolated yield. [b]Values determined by GPC analysis. [c]$M_{n(th.)}$ = ([ε-CL]/2[Ti] × %PCL × 114.14) + ([*rac*-LA]/2[Ti] × %PLA × 144.13) + 32.04 (or 46.08): based on two polymer chains growing from the Ti centre (except complex **6**). Non-immortal mechanism assumed. [d]$M_{n(corr)}$ = (M_n × 0.56 × %CL) + (M_n × 0.58 × %LA). [e]Ratio of ε-CL/*rac*-LA determined by ^{1}H NMR. [f]Average ε-CL and *rac*-LA chain length determined by ^{13}C NMR. [g]Measured using DSC. [h]Measured using the Fox equation: $1/T_{g(th.)} = [W_{LA}/T_{g(rac\text{-}LA)}] + [W_{CL}/T_{g(\varepsilon\text{-}CL)}]$ (where W is the weight%, T measured in Kelvin). [i]2 equivalents EtOH added (relative to [Ti]). [j]2:1 *rac*-LA:ε-CL, 130 °C, 18 h, [monomer]/[Ti] = 600, 0.6 g (4.2 mmol) *rac*-LA, 0.23 mL (2.1 mmol) ε-CL. [k]1:2 *rac*-LA:ε-CL, 130 °C, 18 h, [monomer]/[Ti] = 600, 0.3 g (2.1 mmol) *rac*-LA, 0.46 mL (4.2 mmol) ε-CL.

Upon investigation of the physical properties of these copolymers it is clear from DSC measurements that T_m is often not observed.[13] Only one T_g is observed for each sample confirming the presence of a random copolymer as opposed to a mixture of homopolymers or block copolymers. The T_g measurements complement one of the observed properties of these polymers: at room temperature they are highly elastic in behaviour. Copolymer synthesised using pre-catalyst **5** in the presence of EtOH gives poor M_n, broad PDI and the incorporation of *rac*-LA and ε-CL is 51/49 (Entry 7). However, in this instance T_g closely matches $T_{g(th.)}$, suggesting that the physical properties can closely resemble the theoretical even in the presence of 'undesired' transesterification side reactions. When pre-catalyst **5** is used a transition point is observed at 177.7 °C (onset, Entry 6) and 196.7 °C (Entry 7). The former is close to the T_m of PLA which may reflect the high LA ratio and high L_{LL} value observed for this polymer. The sharp melting observed for Entry 7 is unusual given the low M_n and L_{LL} values but does indicate crystalline polymer. However, on the whole, T_gs do not match that obtained theoretically ($T_{g(th.)}$) using the Fox equation.[20] However, it should be noted that the Fox equation considers the combined ratio of the two homopolymers and does not account for changes that could occur to T_g due to the presence of large amounts of heterobonding. The discrepancies may also be due to the formation of cyclic polymers, which are observed in the low molecular weight washings.[13]

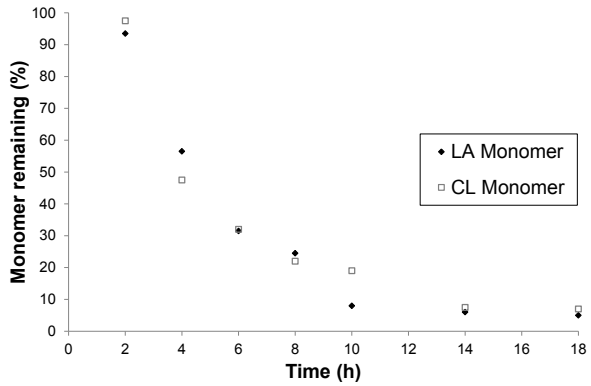


Fig. 1 Monitoring the uptake of monomer into the random copolymer, catalysed by **2**.[21]

Monitoring the reaction of **2** with *rac*-LA and ε-CL in the presence of EtOH shows an even uptake of monomer over the course of the reaction (Figure 1). After four hours, around half of the monomers are consumed whilst a greater percentage of ε-CL has been incorporated compared to *rac*-LA. The even level of monomer consumption over the course of the reaction suggests and reiterates observations made by ^{13}C{^{1}H} NMR spectroscopy *i.e.* transesterification is low and in this case it is not the driving force for randomisation. If transesterification was dominant, or indeed if a gradient polymerisation was taking place, it could be anticipated that rapid incorporation of *rac*-LA would be observed initially, followed by ε-CL as the reaction neared completion. In this case high levels of heterobonding are observed throughout the course of the reaction (Figure 2). The quantity of LA-LA bonds is consistently greater than that of CL-CL bonds, which reflects the longer chain lengths observed using NMR spectroscopy. A comparison of M_n and PDI over the course of the reaction shows a steady growth in M_n which still appears to be increasing as the reaction is quenched after 18 hours (Figure 3). PDI rises modestly during the reaction and is still increasing at the time of quenching.

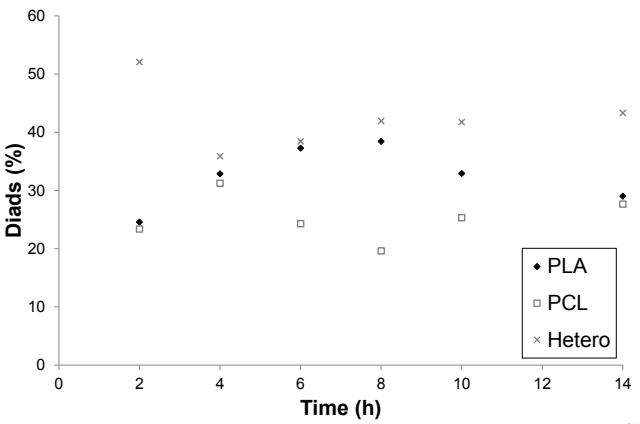


Fig. 2 Comparison of the ratios of diads in the random copolymer.[21]

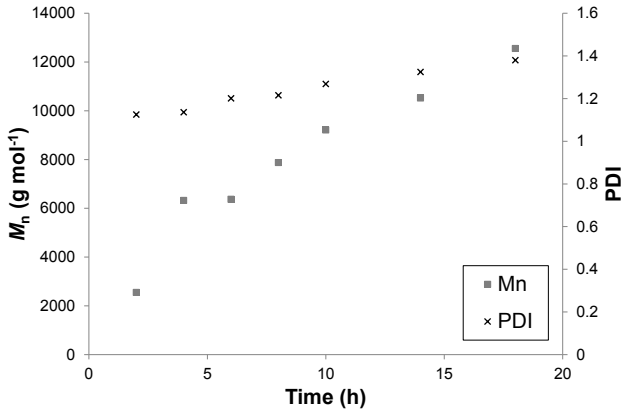


Fig. 3 Change in M_n and PDI over time for the random copolymerisation initiated by **2** (Table 3, Entry 2).

Conclusions

A range of simple, inexpensive titanium complexes have been used in the synthesis of PLA and PCL. Dinuclear complex **6** has shown surprisingly high levels of activity for both PLA and PCL synthesis, but did not offer any real benefits over the AA complexes in terms of the more desirable and challenging random copolymerisation. The attraction of the other systems tested lie in the simplicity of the AA ligand, which allow for rapid synthesis of the complexes and screening in catalysis. They are good pre-catalysts and have been further exploited to provide some of the few examples of random copolymerisations of *rac*-lactide and ε-caprolactone. Moreover, although transesterification is contributing to the process, it is minimal. Reaction monitoring of random copolymerisation catalysed by **2** reveals a steady uptake of both monomers, as opposed to fast uptake of *rac*-LA then redistribution through transesterification. It also revealed that the levels of heterobonding were high throughout, reiterating that this pre-catalyst does not show an extreme preference for *rac*-LA. These pre-catalysts show promise in the synthesis of random copolymers where further investigation should provide an improved and refined method to make random copolymers. Initial studies into the thermal properties of the polymers show very similar T_gs for all the copolymers tested, although further rheological analysis is needed in order to gain greater insight.

Such are the opportunities for variance when using α-AAs as ligands (for example the naked α-AA has been used in this instance) that there are boundless opportunities for complexes with protected and dimerised pro-ligands. Some such complexes have already been described elsewhere,[22] but their competency at polymerisation is yet to be realised. Indeed by introducing a simple dipeptide, which has stronger chelating properties, to a metal alkoxide it is likely that a robust, chiral polymerisation pre-catalyst will be synthesised. These investigations are currently underway and will be reported in due course.

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